REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated June 3, 2004. Upon entry of this Amendment, claims 1-3, 6-9, 11-22, and 24-39 will remain pending in this application with claims 26-30 being withdrawn. New claim 40 is also added. The changes to the claims are fully supported by the specification and original claims. For example, the changes to claims 14 and 32 are supported at *inter alia* page 11, line 19 to page 12, line 24. No new matter is incorporated by this paper. Payment to cover the fee associated with the newly added claim is also submitted herewith.

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Claims 1-9, 11-22, 24, 25, and 31-39 are rejected under 35 U.S.C. § 112, first paragraph, as purportedly not being fully enabled by the specification. Applicants respectfully traverse.

Independent claim 1 has been amended to recite a "Reagent for conjugation to a biomolecule." The specification fully teaches how to use and make such a reagent. Hence, this rejection is overcome and its withdrawal is respectfully requested.

Applicants note that claim 24 was not included in any other rejection. Hence, Applicants are under the understanding that claim 24 is now in condition for allowance. The Examiner's confirmation is respectfully requested.

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Claims 8, 14, and 32 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The Office Action asserts that term "derivative", as it is used in claims 8, 14, and 32, is indefinite. Applicants respectfully traverse.

With respect to claim 8 Applicants respectfully submit the term derivative is defined as "a derivative of avidin or streptavidin having essentially the same binding

function to the affinity ligand." Moreover, the Office Action concedes that "avidin or streptavidin derivatives" is a term of art.

Claim 14 has been amended to recite "at least one amino-carboxy compound". In addition, claim 32 has been amended to recite "the amino-carboxy is EDTA, DTPA, or a derivative thereof having substantially the same bonding properties." Hence, claim 14 no longer recites the term derivative, while the metes and bounds of the term derivative, as it is used in claim 32, is adequately defined.

In view of the above remarks, Applicants submit that this rejection is overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 1-3, 6-9, 11-22, 25, 31, 32 and 34-39 are rejected under 35 U.S.C. § 103(a) as anticipated by Wilbur et al. (WO 97/29114) in view of Wilbur et al. (Bioconjugate Chem. 1997) or in view of Rosenborough (J. Pharm. And Exp. Ther. 1993).

Claim 33 is rejected under 35 U.S.C. § 103(a) as obvious based on Wilbur et al. '114 in view of Wilbur et al. '1997 or Rosenborough, and further in view of Gansoh et al. (U.S. Pat. No. 5,286,850).

These two rejections are addressed together as similar issues apply to both. Moreover, Applicants again respectfully traverse both rejections.

The Office Action asserts that Wilbur '114 describes each feature of the claimed invention except the addition of an N-methyl group or alpha carboxylate in linker 1. The Office Action further asserts that these features are taught by Wilbur '1997 and Resenborough respectively. Moreover, the Office Action concludes that it would have been obvious to modify the reagent of Wilbur '114 by employing an N-methyl group or alpha carboxylate as taught by the secondary references. Applicants respectfully disagree.

Contrary to the assertion in the Office Action, Applicants again submit that the cited documents do in no way teach or fairly suggest introducing an N-methyl group or

alpha carboxylate into linker 1 to thereby stabilize linker 1 against enzymatic cleavage. Moreover, Applicants incorporate all of the arguments asserted in the last Amendment filed to rebut the assertions made in the Office Action. In addition, Applicants also submit herewith a Declaration signed by Dr. D. Scott Wilbur that explains that those of ordinary skill in the art would not interpret the cited documents as teaching or even suggesting employing an N-methyl group or alpha carboxylate in a trifunctional reagent.

For example, Dr. Wilbur explains that it is unreasonable to think that a person of ordinary skill would be taught that an alpha-carboxylate blocks biotinidase cleave of biotinamide bonds by the Rosebrough. This is because Rosenborough fails to prove that carboxylate in the cysteine linker plays a role in blocking biotinidase cleavage. As Dr. Wilbur explains, the Rosenborough study showed that a biotin-cysteine-deferoxamine conjugate had 87% stability towards biotinidase cleavage, and that a biotin-desaminolysyl-deferoxamine conjugate without a linker had 45% stability. Based on this data one could not know that the alpha-carboxylate was responsible for the higher biotinidase stability. The reason is that the results did not answer the question as to whether the biotinidase stability was due to the cysteine linker or came about by having a combination of the cysteine linker and the desferoxamine. Moreover, one could not predict success from the data. The stability of the biotin-desferoxamine adduct itself suggests that there may be something about the desferoxamine that hinders biotinidase cleavage of the biotinamide bond.

Dr. Wilbur further asserts that even if others of skill in the art had made the assumption (but had not been taught) that an alpha-carboxylate was responsible for blocking biotinidase cleavage of biotinamide bonds, and had been taught that an N-methyl blocked biotinidase cleavage from Dr. Wilbur's paper, the combination of this knowledge would not adequately teach or suggest the claimed invention. Dr. Wilbur goes on to explain that there are two very important and interactive factors in the biotin derivatives for

application to a device to remove toxic materials from the blood, and this information is not taught from the literature. One of the factors is the requirement for very high biotinidase stability. The second factor is that biotin derivatives used must retain a very high binding affinity. The stability toward biotinidase cleavage is critical, but it is also essential in the claimed invention that the high binding affinity of the biotin with avidin or streptavidin be retained. For the purpose of using the products of the present invention, the presence of endogenous biotin in serum makes it essential that a high binding affinity be retained so that the biotin conjugate is not displaced from the column by endogenous biotin. Information on how biotin binding with avidin and streptavidin was affected for various modifications of biotin conjugates was not taught from the literature. Dr. Wilbur's later studies established a method for determining the relative binding of biotin conjugates (reported in *Bioconjugate Chemistry* 11, 584-598, 2000) and a large number of biotin derivatives were evaluated to understand how the various modifications affected binding (reported in *Bioconjugate Chemistry* 11, 569-583, 2000). The claimed invention includes these two very important functional aspects. Moreover, none of the cited documents, when taken alone or combined, teach or fairly suggest the claimed invention.

Applicants submit that in view of the above remarks Dr. Wilbur's declaration, both rejections are overcome and withdrawal of both is respectfully requested.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding rejections in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

If any fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this filing, please charge the fees to Deposit Account No. 02-4300; Order No. 033700.003.

If an extension of time under 37 C.F.R. § 1.136 is necessary that is not accounted for in the papers filed herewith, such an extension is requested. The extension fee should be charged to Deposit Account No. 02-4300; Order No. 033700.003.

Respectfully submitted,

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